Case Report

Young patients with endometrial carcinoma selected for conservative treatment: A need for vigilance for synchronous ovarian carcinomas, case report and literature review

Alireza A. Shamshirsaz\textsuperscript{a}, Matthew Withiam-Leitch\textsuperscript{a}, Kunle Odunsi\textsuperscript{b}, Trudy Baker\textsuperscript{b}, Peter J. Frederick\textsuperscript{a}, Shashikant Lele\textsuperscript{b,}\textsuperscript{*}

\textsuperscript{a} Department of Gynecology and Obstetrics, University of Buffalo State University of New York, 219 Bryant Street, Buffalo, NY 14222, USA
\textsuperscript{b} Department of Gynecologic Oncology, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263, USA

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Abstract

Background. The aim of this paper is to report a case of synchronous ovarian malignancy in a very young patient with early endometrial cancer who desired fertility-sparing management.

Case. Twenty one-year-old patient presented with an apparent early stage endometrial cancer and desiring conservative management. After failure of conservative management for 3 years, surgery was performed. An incidentally small papillary serous ovarian tumor of low malignant potential was found.

Conclusion. Careful preoperative and intraoperative assessment of the adnexa is mandatory in young women with endometrial cancer. Those who desire ovarian preservation should be counseled regarding the high potential for coexisting ovarian malignancy.

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Keywords: Endometrial carcinoma; Ovarian carcinoma; Synchronous tumors; Conservative treatment

Introduction

In the United States endometrial cancer is the most common malignancy of the female genital tract, with 40,880 new cases and 7310 cancer-related deaths estimated in 2005 [1]. Although endometrial cancer tends to be diagnosed in older, postmenopausal women with a mean age of 61 years, between 5% and 29% of endometrial cancers are diagnosed in “young” women [2–5].

For young patients who desire future fertility, conservative management of uterine cancer has been advocated as a safe alternative to hysterectomy and bilateral salpingo-oophorectomy by a number of groups [6,7]. In fact, conservative therapy has led to successful pregnancies in a number of patients [8]. Clearly, accurate histological staging is mandatory so that only patients with early stage, well differentiated tumor are selected. Furthermore, appropriate follow-up protocols need to be developed so that recurrences can be detected early to reduce long-term morbidity and mortality.

This is a case report of a young woman treated conservatively for well differentiated endometrial adenocarcinoma. She was also found to have a synchronous ovarian serous cystadenocarcinoma of low malignant potential. This case report and review of the literature demonstrates the need not only for careful surveillance for local recurrence of uterine disease, but also for synchronous tumors of the ovary.

Case report

The patient was a 21-year-old G0P0 who presented to her primary care physician with increased fatigue and malaise. The patient was morbidly obese (251 lb., BMI=36.2) and had a history of irregular, heavy menses. She was admitted to the
hospital for transfusion due to hemoglobin of 5.6 mg/dl. The patient was started on oral contraceptives to regulate her menses. Five weeks later she presented to her gynecologist with profuse bleeding and again was severely anemic with hemoglobin of 5.3. Pelvic ultrasound revealed a thickened endometrium with possible polyps and a 3 cm intramural fibroid. The ovaries were unremarkable. An emergency dilatation and curettage with hysteroscopy was performed which showed profuse, vascular endometrial overgrowth. Pathology revealed endometrioid adenocarcinoma, FIGO grade 1, occurring in a setting of complex hyperplasia with atypia.

The management options were discussed with the patient. She declined surgery because she wanted preservation of fertility. Therefore, she was started on megestrol acetate 80 mg twice daily. The patient was then followed with endometrial biopsies every 3 months. After 6 months of megestrol acetate the patient developed depression and was switched to medroxyprogesterone 10 mg daily for 14 days of each month. Twelve months after presentation the patient had an endometrial biopsy that showed proliferative endometrium. Dilatation and curettage with hysteroscopy revealed complex hyperplasia with atypia. The medroxyprogesterone dose was increased to 10 mg twice daily for 14 days of each month, and the patient continued to be followed with endometrial biopsies every 3 months. Subsequent endometrial biopsies confirmed the resolution of the endometrial hyperplasia.

Thirty-two months after presentation an endometrial biopsy revealed atypical hyperplasia with squamous morules. The medroxyprogesterone was increased to 10 mg three times daily for 14 days in each month. Thirty-six months after presentation the endometrial biopsy revealed atypical hyperplasia with squamous morules. The medroxyprogesterone dose was increased to 10 mg twice daily for 14 days of each month, and the patient continued to be followed with endometrial biopsies every 3 months. Subsequent endometrial biopsies confirmed the resolution of the endometrial hyperplasia.

An MRI was performed which revealed superficial invasion compatible with early stage IB disease and polycystic ovaries.

At this point definitive surgery was performed with exploratory laparotomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy and pelvic washing. Frozen section revealed a well-differentiated endometrioid adenocarcinoma with 20% invasion of the myometrial wall. The ovaries were reported as polycystic with no evidence of malignancy. The permanent pathology revealed an endometrioid adenocarcinoma, histological grade 2, and involving 80% of the myometrial thickness. The tumor extended onto the upper endocervical canal surface with no invasion of the endocervical or cervical stroma (Stage IIA, grade 2). There was no lymph vascular invasion. The right ovary was normal except for polycystic changes. However, pathology on the left ovary revealed a papillary serous ovarian tumor of low malignant potential. The tumor was well encapsulated and was a 0.5 cm lesion found within a 1.2 cm cyst. Pelvic washing was negative.

The patient was treated with postoperative pelvic radiation, total of 5040 cG. The patient remains without evidence of disease 9 months following surgery.

**Discussion**

Conservative management of endometrial cancer in young patients desiring fertility has been successfully employed in numerous reports [6–8]. Our case report demonstrates two important caveats to conservative treatment of endometrial cancer that need to be addressed. First, an appropriate surveillance strategy needs to be employed to detect local recurrence of endometrial cancer. Second, there is a need for increased

### Table 1

<table>
<thead>
<tr>
<th>Author, reference</th>
<th>Year</th>
<th>Median age</th>
<th>Total</th>
<th>E/E (%)</th>
<th>E/NE (%)</th>
<th>NE/E (%)</th>
<th>NE/NE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eifel et al.</td>
<td>1981</td>
<td>41</td>
<td>29</td>
<td>16 (55%)</td>
<td>2 (7%)</td>
<td>–</td>
<td>11 (38%)</td>
</tr>
<tr>
<td>Crissman et al.</td>
<td>1981</td>
<td>36</td>
<td>6</td>
<td>4 (66%)</td>
<td>2 (33%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Choo et al.</td>
<td>1982</td>
<td>55</td>
<td>49</td>
<td>26 (53%)</td>
<td>21 (43%)</td>
<td>1 (2%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Zaino et al.</td>
<td>1984</td>
<td>60</td>
<td>24</td>
<td>13 (54%)</td>
<td>9 (38%)</td>
<td>2 (15%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Ulbrigith et al.</td>
<td>1988</td>
<td>55</td>
<td>11</td>
<td>6 (55%)</td>
<td>–</td>
<td>–</td>
<td>5 (45%)</td>
</tr>
<tr>
<td>Jambhekar et al.</td>
<td>1988</td>
<td>46</td>
<td>17</td>
<td>15 (88%)</td>
<td>2 (12%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Eisner et al.</td>
<td>1989</td>
<td>–</td>
<td>11</td>
<td>5 (45%)</td>
<td>6 (55%)</td>
<td>5 (45%)</td>
<td>–</td>
</tr>
<tr>
<td>Puira et al.</td>
<td>1989</td>
<td>51</td>
<td>5</td>
<td>1 (20%)</td>
<td>4 (80%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Montoya et al.</td>
<td>1989</td>
<td>54</td>
<td>37</td>
<td>23 (62%)</td>
<td>4 (11%)</td>
<td>10 (27%)</td>
<td>8 (serous)</td>
</tr>
<tr>
<td>Prat et al.</td>
<td>1991</td>
<td>–</td>
<td>9</td>
<td>6 (66%)</td>
<td>3 (33%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Pearl et al.</td>
<td>1993</td>
<td>51</td>
<td>16</td>
<td>14 (88%)</td>
<td>1 (6%)</td>
<td>1 (7%)</td>
<td>–</td>
</tr>
<tr>
<td>Shue et al.</td>
<td>1995</td>
<td>51</td>
<td>6</td>
<td>5 (83%)</td>
<td>1 (16%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Zaino et al.</td>
<td>2001</td>
<td>49</td>
<td>74</td>
<td>64 (86%)</td>
<td>3 (4%)</td>
<td>1 (1%)</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>Soliman et al.</td>
<td>2004</td>
<td>50</td>
<td>77</td>
<td>57 (74%)</td>
<td>20 (26%)</td>
<td>11 (serous)</td>
<td>–</td>
</tr>
<tr>
<td>Walsh et al.</td>
<td>2005</td>
<td>41</td>
<td>23</td>
<td>22 (96%)</td>
<td>1 (4%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>394</td>
<td>277</td>
<td>74 (19%)</td>
<td>3 (0.8%)</td>
<td>34 (9%)</td>
<td>19 (serous)</td>
</tr>
</tbody>
</table>

* a E/E=endometrioid, mixed-endometrioid in uterus/endometrioid, mixed-endometrioid in ovary.
* b E/NE=endometrioid, mixed-endometrial in uterus/no endometrioid (clear cell, mucinous, serous including papillary serous, transitional (Brenner), undifferentiated) in ovary.
* c NE/E=no endometrioid (serous, clear cell, mucinous, miscellaneous) in uterus/endometrioid, mixed-endometrioid in ovary.
* d NE/NE=no endometrioid in uterus/no endometrioid in ovary.
* e Included patients with disseminated disease at the time of diagnosis.
* f Seven patients excluded from this study because of unclear histology.
* g Indicates only ovarian histology.
vigilance for the development of synchronous tumors of the ovary, even in the very young patient.

The most common agents used for conservative treatment of endometrial cancer are the progestins medroxyprogesterone acetate and megestrol acetate with response rates of 51–75% [7,9]. Most of the patients with recurrences experienced them within approximately 1 year after the completion of their progestin treatment. However, as shown in our case, recurrence can occur several years later even with continued use of progestins. This highlights the need for a frequent and long-term endometrial sampling strategy. In our case, we elected to perform endometrial biopsy every 3 months, with dilatation and curettage with hysteroscopy for abnormal results.

The issue of synchronous ovarian tumors in young patients with endometrial cancer is controversial. Synchronous primary cancers of endometrium and ovary occur in approximately 5% of all women with endometrial cancer [10]. However, there are also reports of a higher incidence of ovarian malignancies in subsets of young women who may be considering uterine or ovarian preservation, with a range of 5–29% reported in previous articles [2–5,11]. Crissman et al. found coexisting tumors in 6 of 32 (18.8%) young patients [2]. Recently, Gitch et al. and Evans-Metalf et al. noted significantly higher rates in young (11 and 29%) compared with older women (4.6% and 2% respectively) [3,4]. Furthermore, Walsh et al. found 19% and Duska et al. found 10% synchronous ovarian malignancies in women younger than 45 years [5,11].

Even intraoperative assessment of ovarian pathology can be flawed. Walsh et al. reported four patients (9%) with benign appearing ovaries at the time of surgery that were then found to have tumor in the adnexa on final pathologic examination, similar to our patient [11]. Risk of occult malignancy harbored in grossly normal-appearing ovaries in young women has also been reported by Evan-Metalf et al. [4].

In the general population, endometrioid histology accounts for 16–20% of the epithelial ovarian carcinoma. As seen in Table 1, the most common histology in synchronous endometrium and ovary has been endometrioid (70%) [2,10–23]. Patients with concomitant endometrioid and serous ovarian tumor comprised only 17%. The patients with synchronous dual primary ovarian and endometrial carcinoma tended to be 10–20 years younger than their counterparts with ovarian or endometrial carcinoma [23]. Various criteria have been proposed to distinguish between ovarian metastases and independent primaries in women with endometrial cancer. In most studies diagnosis of synchronous arising tumor was assigned based upon superficial or no myometrial invasion, low grade and stage of endometrial tumor, low grade and stage of the ovarian tumor, dissimilar grades and stage of the ovarian tumor, dissimilar grades between the uterine and ovarian sites, or dissimilar tumor histology based upon Ulbright et al. study [15]. The ova is a known site of metastatic spread from the uterus, and coexisting tumor in the ovary, particularly if it is of endometrioid histology, could represent endometrial metastasis. There has been uniform agreement that survival in cases of synchronous neoplasm of ovary and endometrium is surprisingly excellent. This relatively good survival has been used to argue that these tumors often represent separate primaries [10,12].

The cause of the simultaneous arising neoplasm has not yet been elucidated. It has been suggested that embryological similar tissues, such as those of the female genital tract, may be subject to the same carcinogenic or hormonal stimuli and thereby develop synchronous neoplasm. Furthermore, several molecular studies have supported the hypothesis of independent origins by demonstrating different patterns of X chromosome inactivation and dissimilar mutations in PTEN, P53, or K-ras [24–26].

Hereditary nonpolyposis colorectal cancer (HNPCC), or Lynch syndrome, is one of the most common familial cancer syndromes due to a defect in a DNA mismatch repair gene, usually a germline mutation in hMLH1 or hMSH2 [27]. Watson et al. reported that HNPCC patients with ovarian cancer are more likely to have a synchronous endometrial cancer than other ovarian cancer patients [28]. However, our patient in her genetic consult did not meet the Amsterdam criteria (II) for HNPCC [27].

Borderline tumors (low malignant potential) account for 10–20% of ovarian epithelial tumors and the average age at diagnosis is at the mid-40s [29]. The majority of borderline tumors are serous. Approximately 75% of patients are diagnosed with stage I disease [29,30]. We found only two studies (Castro et al. with two cases and Chamber et al. with three cases) that mentioned synchronous borderline ovarian tumors with endometrial cancer [31,32]. However, it is possible that many authors categorized these tumors as grade I disease.

Numerous difficulties are encountered when faced with decisions concerning the conservative treatment of endometrial adenocarcinoma in young women desiring to maintain their fertility. Many women who have early endometrioid cancers as a result of unopposed estrogenic stimulation either cannot take or will not tolerate systemic progestosterone because of associated adverse effects [33]. For these individuals, intrauterine progestosterone may induce the desired antineoplastic actions, potentially avoiding any associated systemic adverse effects [34]. We would recommend a cautious approach. The high incidence of synchronous malignancy in the ovaries suggests an increased susceptibility of the reproductive organs to carcinogenic transformation.

We would suggest the need for a heightened awareness and the possibility of using MRI and ultrasound preoperatively or performing a frozen section intraoperatively and potentially the use of laparoscopy to rule out adnexal pathology. We also recommend continuous follow-up in young patients with preserved ovaries after hysterectomy. We must bear in mind, however, that any delay in surgery could increase the recurrence rate or the development of metastases, which could potentially worsen the prognosis.

References


